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(54) Process for the preparation of S(+)-6-methoxy-alpha-methyl-2-naphtalene-acetic acid.

(57) The invention relates to a process for the preparation of S(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid by resolution of R,S-6-methoxy-α-methyl-2-naphthalene-acetic acid. According to the invention R,S-6-methoxy-α-methyl-2-naphthalene-acetic acid and R(-)-2-amino-1-butanol are dissolved in water at 40-60 °C. Then the solution thus obtained is cooled to 25-35 °C. Subsequently the obtained solution is grafted with a salt of S(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid and R(-)-2-amino-1-butanol, further it is cooled to 5-15 °C. The thereby formed crystals are separated from the solution and washed with water and subsequently hydrolyzed by adding a strong acid, whereby S(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid crystallizes and the obtained crystals are separated from the mother lye and the R(-)-6-methoxy-α-methyl-2-naphthalene-acetic acid present in the crystallization-mother lye is racemized by heating, which racemate solution can be reused as starting material.

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The invention relates to a process for the preparation of S(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid by resolution of R,S-6-methoxy-α-methyl-2-naphthalene-acetic acid.

It is noted that for simplicity the compound S-(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid will be abbreviated to S(+)M.M.N.A., and the compound R,S-6-methoxy-α-methyl-2-naphthalene-acetic acid will be abbreviated to R,S M.M.N.A.

S(+)M.M.N.A. is an important medicine known by the name of Naproxene. There are known a number of resolution methods of R,S M.M.N.A. which are used for about 20 years on an industrial scale. It is noted that the S(+)-compound is disproportionately more expensive than the R,S compound. The known resolution methods have the following disadvantages.

- One uses optically active bases which are often more expensive.
- The optically active bases used for the resolution often have one relatively high molecular weight so as to require much resolution agent.
- The formed salts normally crystallize very finely so that the separation from the crystallization liquid and the washing of the salt are not well to practice. Usually a recrystallization is to be done of the salt to obtain sufficient optical purity.
- The resolutions are carried out in solvents. Pollutions accumulate in the recrystallization liquid. Good resolutions are difficult to carry out from the polluted solutions. When the resolution is to be carried out in a solution this means that the crystallization liquid is quickly polluted and cannot be reused indefinitely.

Prior Art

The best known preparation methods of S(+)-M.M.N.A. are the resolution of R,S, M.M.N.A. with Cinchonidine and the resolution of R,S M.M.N.A. with S(-)-α-phenyl-ethylamine.

The resolution of R,S M.M.N.A. with Cinchonidine in various variants is described in many patents, a.o. in U.S. 3.683.015 and E.P. 44.984. The resolution with Cinchonidine has the following disadvantages: Cinchonidine is expensive, has a high molecular weight, is toxic, which requires extra precautions in preparing a medicine, the salt of S-(+)M.M.N.A. and Cinchonidine crystallizes very finely, causing filtration problems and there has to be worked in solvents.

The resolution of R,S M.M.N.A. with S(-)-α-phenylethylamine is known from several patents a.o. in E.P. 132.854 and J.P. 8036429.
S(-)-α-phenylethylamine is a rather expensive resolution agent, there has to be crystallized twice to obtain sufficient optical purity and one has to crystallize from sometimes very toxic solvents (for example chloroform).

The invention has the object of providing a new resolution technique whereby the above-mentioned disadvantages of the known resolution methods are efficiently avoided.

Hereto the invention provides a process for the preparation of S(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid by resolution of R,S-6-methoxy-α-methyl-2-naphthalene-acetic acid, characterized in that R,S-6-methoxy-α-methyl-2-naphthalene-acetic acid and R(-)-2-amino-1-butanol are dissolved in water at 40-60 °C, followed by cooling to 25-35 °C, whereafter the obtained solution is grafted with the salt of S(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid and R(-)-2-amino-1-butanol, is further cooled to 5-15 °C and the so formed crystals are separated from the solution, washed with water and subsequently hydrolyzed by adding a strong acid, whereby S(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid crystallizes and the obtained crystals are separated from the mother lye, and the R(-)-6-methoxy-α-methyl-2-naphthalene-acetic acid present in the crystallization mother lye is racemized by heating which racemization solution may be reused as starting material.

According to the present process R,S M.M.N.A. is split by crystallizing a salt of S(+)M.M.N.A. and R(-)-2-amino-1-butanol from an aqueous solution of R,S M.M.N.A. and R(-)-2-amino-1-butanol. The great advantages of this method of the invention are: R(-)-2-amino-1-butanol is very cheap it is a byproduct of the preparation of the medicine Ethambutol; it has a relatively low molecular weight so that relatively little is needed, and it can be recovered and reused. Furthermore it is a stable compound.

Furthermore, it is very attractive that the salt of S(+)M.M.N.A. and R(-)-2-amino-1-butanol formed during the resolution crystallizes in large crystals so as to enable an optically pure product to be obtained by crystallizing only one time.

Also, the resolution is carried out in aqueous medium giving a great advantage.

After a resolution one wishes preferably in the crystallization mother lye to directly racemize the solved, non-desired enantiomere and subsequently, after adding a new portion of R,S-compound and the recovered splitting agent, to reuse the solution for a following crystallization and to repeat this indefinitely.

It has appeared that the resolutions of R,S M.M.N.A. by crystallization with an optically active base are very sensitive for pollutions with the crystallization liquid.

When crystallizing from a polluted liquid, said

crystallization will be retarded and the crystals remain small and poor optical purity is reached whereby recrystallization of the formed salt is required.

When the resolution is to be carried out in a solvent, decomposition products and technical pollutions accumulate therein whereby the solutions cannot be often reused. Because the process of the invention is worked in aqueous medium, the decomposition products and technical pollution can be easily removed from the aqueous solution by filtration with active carbon whereby the solution can be used practically indefinitely. One does not have this possibility when using solvents.

It is noted that the German patent 2008272 in general terms indicates that R(-)-2-amino-1-butanol besides 36 other optical active bases are suitable for the resolution of R,S M.M.N.A. by crystallization of the salt of S(+)M.M.N.A. and R(-)-2-amino-1-butanol from solvents. This document is silent about crystallization from an aqueous solution.

The said patent does not give any data and does not give an example directed to the specific use of R(-)-2-amino-1-butanol. It has also appeared that in the solvents mentioned in the respective patent no good solution of R,S M.M.N.A. with R(-)-2-amino-1-butanol is possible because the salt of S(+)M.M.N.A. and R(-)-2-amino-1-butanol and also a portion of the salt of R(-) M.M.N.A. and R(-)-2-amino-1-butanol crystallizes. There is no sufficient selectivity in the solvents to obtain an optically pure product.

As mentioned earlier, the invention crystallizes from an aqueous solution wherein the salts of S-(+)M.M.N.A. and R(-) M.M.N.A. with R(-)-2-amino-1-butanol have sufficient difference in solubility to enable resolution.

In the patent IT 2368984 a method is described wherein also a.o. R(-)-2-amino-1-butanol is used. For the resolution not the simply formed and hydrolyzed salt of S(+)M.M.N.A. and R(-)-2-amino-1-butanol is crystallized but the amide of S(+)-M.M.N.A. and R(-)-2-amino-1-butanol. This means that several chemical syntheses extra have to be carried out.

So the acid chloride on an ester has to be made from R,S M.M.N.A., subsequently the amide has to be formed with R(-)-2-amino-1-butanol and after the resolution the amide has to be hydrolyzed.

In the process of the invention the salt of S(+)-M.M.N.A. and R(-)-2-amino-1-butanol os formed spontaneously in the aqueous medium and the obtained salt is simply hydrolyzed in aqueous medium with a strong acid.

Now the process of the invention is further explained.

First a solution is made from R,S M.M.N.A. and R(-)-2-amino-1-butanol in warm water at 40-60 °C in a nearly equimolar proportion. Subsequently, the so obtained solution is slowly cooled to 25-35 °C. At the temperature at which the saturation point is reached, the solution is grafted with the salt of S-(+)M.M.N.A. and R(-)-2-amino-1-butanol. By further cooling the solution to 5-15 °C the salt of S(+)-M.M.N.A. and R(-)-2-amino-1-butanol begins to crystallize. It has appeared to be important that crystallizing is such that no large oversaturation of the solution takes place since in such a case also the salt of the R(-) enantiomere appears to crystallize whereby the required good optical purity is not obtained.

It has appeared that sufficient grafting is required whereas cooling of the solution should occur slowly and uniformly.

It has appeared to be possible to replace a portion of the R(-)-2-amino-1-butanol by another base like NaOH or KOH. By adding another base it has appeared that the salt of the not desired enantiomere crystallizes less quickly and a higher productivity of the resolution can be obtained.

After the end of the crystallization the formed crystals, large needles, are separated from the liquid by filtration and washed with water.

The separated salt subsequently is solved in warm water and hydrolyzed by adding a strong acid for example sulphuric acid whereby S(+)-M.M.N.A. crystallizes which subsequently is separated by filtration from the mother lye.

In the hydrolysis-mother lye the sulphate of R(-)-2-amino-1-butanol is present in solution which after making alkaline the liquid can be extracted from the solution by a suitable solvent.

In the crystallization-mother lye is solved a portion of the salt of R,S M.M.N.A. and R(-)-2-amino-1-butanol and the salt of R(-)M.M.N.A. and R(-)-2-amino-1-butanol. The R(-)M.M.N.A. can be directly racemized in the crystallization-mother lye to R,S M.M.N.A. by heating. In aqueous medium the racemization speed is rather low. By adding an alcohol the racemization speed can be considerably increased whereby the racemization temperature can be lower and the racemization time shorter.

After the racemization the added alcohol is distilled. The remaining solution of R,S M.M.N.A. and R(-)-2-amino-1-butanol is now purified by filtration with active carbon whereby it is possible to reuse the solution practically indefinitely for crystallization after adding a new portion of R,S M.M.N.A. and the R(-)-2-amino-1-butanol recovered from the hydrolysis-mother lye.

The above described method is schematically represented by the drawing.

Finally the present invention is further explained by the following non-limiting examples.

EXAMPLE I

In a flask of 100 cm^3 60 cm^3 of water 12 g of R,S- M.M.N.A. and 4,8 g of R(-)-2-amino-1-butanol were transferred and mixed.
The obtained mixture was heated to about 50 °C, to dissolve R,S- M.M.N.A. The mixture was slowly cooled to about 30 °C.

At this temperature 0,2 g of finely ground salt of S(+)M.M.N.A. and
R(-)-2-amino-1-butanol were added.
After grafting recrystallization took place whereafter the mixture during 5 hours under stirring was uniformly cooled to about 10 °C. It was for an hour stirred at about 10 °C whereafter the crystals were filtered and washed on the filter with little water of about 0 °C.

The obtained crystals were solved in 40 cm^3 of water of about 60 °C. Now under stirring 20 %'S sulphuric acid was dosed until a pH of about 1 was reached. During dosing the diluted sulphuric acid the product crystallized. The mixture was cooled to about 25 °C and the crystallized product was filtered, washed with water and dried.
1,9 g of white crystalline substance was obtained. The specific rotation was: $\alpha \frac{20}{D}$: + 62 (C = 1 % in chloroform).

Example II

Crystallization.

In a flask of 500 cm^3 were mixed 280 cm^3 of water, 2,8 g of NaOH and 22 g of R(-)-2-amino-1-butanol. The so obtained mixture was heated to about 55 °C, whereafter 67,5 g of R,S M.M.N.A. were added. After obtaining a solution the same was cooled to about 32 °C. At this temperature the solution was grafted with 1,5 g of very finely ground salt of S(+)M.M.N.A. and R(-)-2-amino-1-butanol.
After grafting the crystallization began. Subsequently, under agitation during 7 hours the temperature was decreased to about 6 °C. For 2 hours agitating was done at about 6 °C and the formed crystals were filtered and washed with little cold water.

Hydrolysis of the obtained salt.

The obtained salt was dissolved in 225 cm^3 of water of about 60 °C. Under stirring at 60 - 70 °C during about 2 hours 20% sulphuric acid was dosed until a pH lower than 1,5 was obtained. Now the solution was cooled to about 25 °C and the white crystalline substance crystallized during dosing of the diluted sulphuric acid was filtered, washed with water and dried.

Hereby 17,4 g of a white crystalline product was obtained. The obtained product at analysis appeared to have a specific rotaion of $\alpha \frac{20}{D}$: + 63,8 (C = 1 in chloroform).

Recovering of R(-)-2-amino-1-butanol.

In the mother lye of the foregoing hydrolysis (the foregoing step) was dissolved the sulphate of R(-)-2-amino-1-butanol. To the hydrolysis mother lye under stirring ca. 8 g of NaOH was added and after solution about 35 g of NaCl was added. After dissolution of the NaCl the obtained solution was extracted five times in a separation funnel with each time 40 cm^3 of isobutyl alcohol.
The collected extracts, in total 192 cm^3, were evaporated in a rotating vacuum drier.
A distillation residue, the recovered R(-)-2-amino-1-butanol, was obtained in an amount of about 6,1 g.
The product appeared to have a specific rotation of:
a $\frac{20}{D}$: - 15,8 (C = 1 in 1 N hydrochloric acid).

Racemization:

In the mother lye of the crystallization in dissolved state is present a mixture of R,S M.M.N.A., R(-)M.M.N.A. and R(-)-2-amino-1-butanol.
To the crystallization-mother lye (+ wash water), in total 335 cm^3, 335 cm^3 of tertiary butanol were added and the obtained mixture was kept, in an autoclave about 22 hours at about 140 °C. After cooling of the mixture a sample of about 5 cm^3 was taken, diluted with about 20 cm^3 water and acidified to a pH of about 1 with 20 % sulphuric acid whereby a white crystalline product R,S M.M.N.A. was obtained.
After filtering, washing with water and drying the specific rotation was determined. The $\alpha \frac{20}{D}$ was -0,3 which means that the racemization was nearly complete. Subsequently the racemization mixture in a flask of 1 l was provided with a spike mount and distillation cooler, subjected to distillation until the boiling temperature of the mixture in the flask was higher than about 99 °C.
Then the remaining aqueous racemization liquid in the flask was cooled to about 25 °C and the 6,1 g of recovered R(-)-2-amino-1-butanolwere added. Subsequently 4 g active carbon was added whereafter stirring was continued for 15 minutes. Thereafter the active carbon was separated by filtration from the mixture. The now almost colourless solution was supplemented with little water to a volume of 330 cm^3. This liquid was reused for a following crystallization.

Example III.

In a flask of 500 cm^3 the 330 cm^3 purified racemic liquid to which was added the recovered R(-)-2-amino-1-butanol, was stirred.
The liquid was heated to about 55 °C, whereafter a mixture of 0,2 g of NaOH, 1,1 g R(-)-2-amino-1-butanol and 17,0 g of R,S M.M.N.A was added. Stirring was continued until a solution was obtained which subsequently was cooled to about 32 °C. Subsequently grafting was done and crystallization like in Example II. The resolution can practically be repeated indefinitely.

Claims

1. A process for the preparation of S(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid by resolution of R,S-6-methoxy-α-methyl-2-naphthalene-acetic acid **characterized** in that R,S-6-methoxy-α-methyl-2-naphthalene-acetic acid and R(-)-2-amino-1-butanol are dissolved in water at 40-60 °C, followed by cooling to 25-35 °C, whereafter the obtained solution is grafted with a salt of S(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid and R(-)-2-amino-1-butanol, further it is cooled to 5-15 °C and the thereby formed crystals are separated from the solution and washed with water and subsequently hydrolyzed by adding a strong acid, whereby S(+)-6-methoxy-α-methyl-2-naphthalene-acetic acid crystallizes and the obtained crystals are separated from the mother lye and the R(-)-6-methoxy-α-methyl-2-naphthalene-acetic acid present in the crystallization-mother lye is racemized by heating, which racemate solution can be reused as starting material.

2. Method of claim 1, **characterized** in that the hydrolysis is carried out with H_2SO_4 as strong acid.

3. Method of claim 1 or 2, **characterized** in that crystallizing is carried out with a mixture of R(-)-2-amino-1-butanol and a base.

4. Method of claim 3, **characterized** in that as base NaOH or KOH is used.

WORKİNG SCHEME